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Sommario	The evolution of Acute Myeloid Leukemia (AML) is a complex process characterized by the stepwise accumulation of mutations, primarily occurring in Hematopoietic Stem Cells (HSCs). Such mutations give rise to the so-called Leukemia Initiating Cell (LIC), characterized by enhanced self-renewal and impaired differentiation. The molecular mechanisms underlying this transition are still poorly understood but they are likely to be critical to understanding the leukemic stem cell (LSC) biology. Recent functional and genetic studies on AML revealed NPMc+ as a critical driver oncogene, highly conserved at relapse, and characterizing the AML phenotype. Likely, NPMc+ has a pivotal role in the LIC evolution and LSC behavior. Taking advantage of the extended pre-leukemic phase of our inducible NPMc+ mouse model, we elucidated the impact of NPMc+ expression on normal HSCs to define the early mechanisms of NPMc+ induced leukemogenesis. We have found that NPMc+ expression leads to the expansion of the HSC compartment by enforcing a stem-cell transcriptional program that promotes quiescence and increases self-renewal. Moreover, considering the strong co-occurrence of NPMc+ with FLT3-ITD in patients, we investigated the mechanisms of this cooperation in pre-leukemia. Strikingly, the expression of NPMc+ in the FLT3-ITD background i) prevents the HSCs exhaustion imposed by FLT3-ITD, ii)

	restores their repopulating capacity, iii) restores the same transcriptional program observed in the NPMc+ HSCs, including quiescence genes upregulation. These data strongly suggest that NPMc+ and FLT3-ITD mutations cooperate in inducing AML, thanks to the NPMc+ ability to limit LT-HSCs exhaustion and reconstitute a fully competent LT-HSC population in which the oncogenic activities of FLT3-ITD lead to a rapid selection of the LICs. We thus hypothesized that enforced quiescence might be critical to maintain the transformed clone during both the pre-leukemic and the leukemic phase. In support, we xi identified the TGFβ pathway, one of the most critical pathways that regulate HSCs quiescence, as being upregulated by NPMc+, either alone or in combination with FLT3- ITD. Moreover, we report that pharmacological inhibition of this pathway impacts on NPMc+/FLT3-ITD AML growth in vivo. Finally, we provide preliminary results suggesting that TGFb inhibition might modify the fitness and/or the number of LSCs.
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